Histone deacetylase 7, a potential target for the antifibrotic treatment of systemic sclerosis

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Abstract: OBJECTIVE: We have recently shown a significant reduction in cytokine-induced transcription of type I collagen and fibronectin in systemic sclerosis (SSc) skin fibroblasts upon treatment with trichostatin A (TSA). Moreover, in a mouse model of fibrosis, TSA prevented the dermal accumulation of extracellular matrix. The purpose of this study was to analyze the silencing of histone deacetylase 7 (HDAC-7) as a possible mechanism by which TSA exerts its antifibrotic function. METHODS: Skin fibroblasts from patients with SSc were treated with TSA and/or transforming growth factor beta. Expression of HDACs 1-11, extracellular matrix proteins, connective tissue growth factor (CTGF), and intercellular adhesion molecule 1 (ICAM-1) was analyzed by real-time polymerase chain reaction, Western blotting, and the Sircol collagen assay. HDAC-7 was silenced using small interfering RNA. RESULTS: SSc fibroblasts did not show a specific pattern of expression of HDACs. TSA significantly inhibited the expression of HDAC-7, whereas HDAC-3 was up-regulated. Silencing of HDAC-7 decreased the constitutive and cytokine-induced production of type I and type III collagen, but not fibronectin, as TSA had done. Most interestingly, TSA induced the expression of CTGF and ICAM-1, while silencing of HDAC-7 had no effect on their expression. CONCLUSION: Silencing of HDAC-7 appears to be not only as effective as TSA, but also a more specific target for the treatment of SSc, because it does not up-regulate the expression of profibrotic molecules such as ICAM-1 and CTGF. This observation may lead to the development of more specific and less toxic targeted therapies for SSc.

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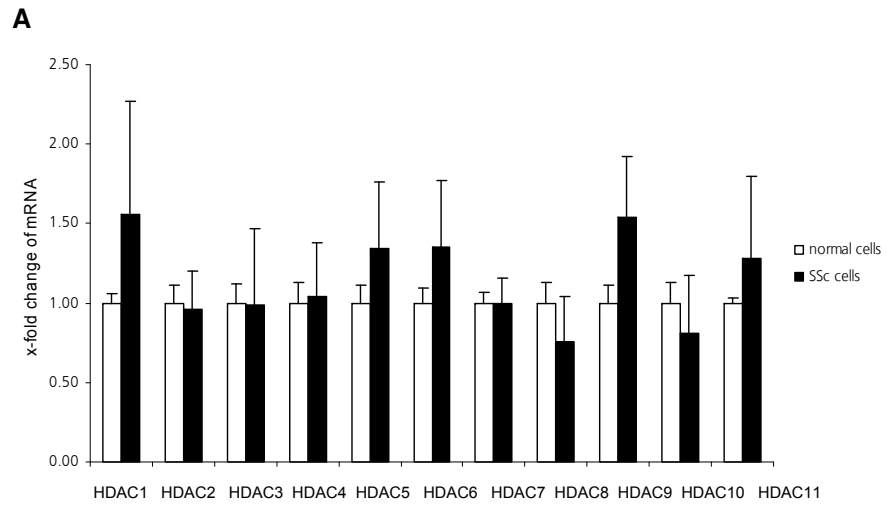
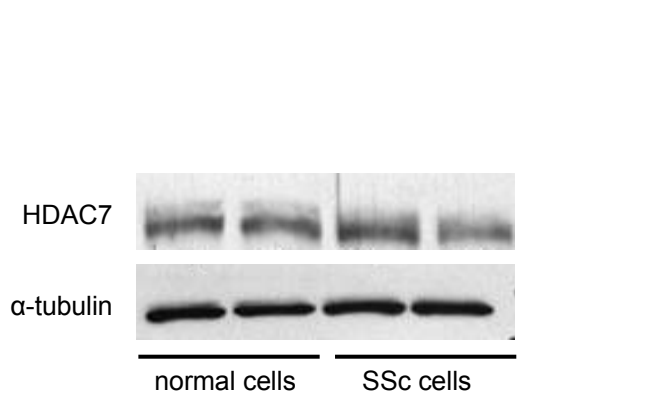
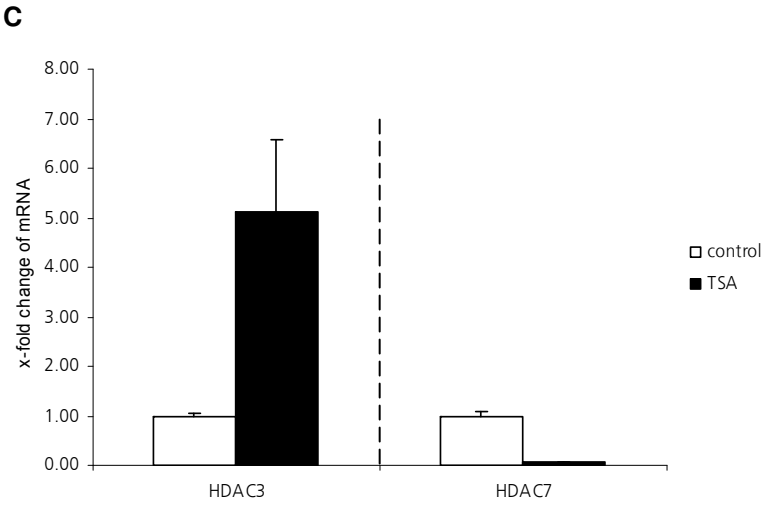
Figure 1


A
2.50
2.00
1.50
1.00
0.50
0.00
x-fold change of mRNA
normal cells
SSc cells
HDAC1
HDAC2
HDAC3
HDAC4
HDAC5
HDAC6
HDAC7
HDAC8
HDAC9
HDAC10
HDAC11


B
HDAC7
α-tubulin
normal cells
SSc cells


C
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
x-fold change of mRNA
control
TSA
HDAC3
HDAC7

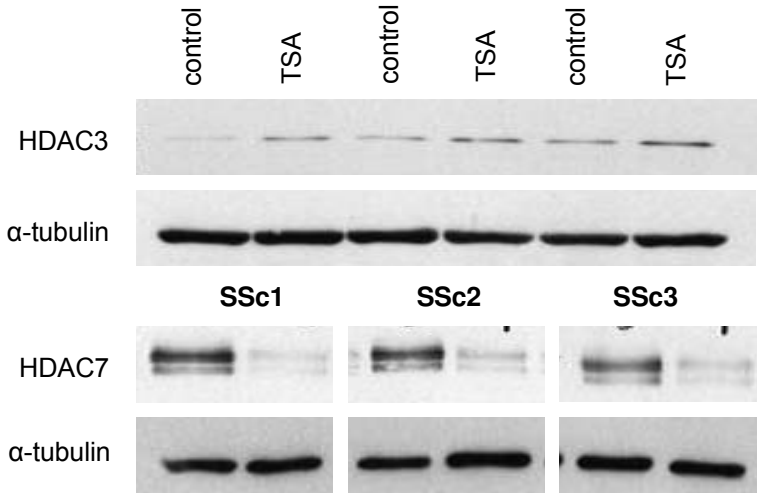
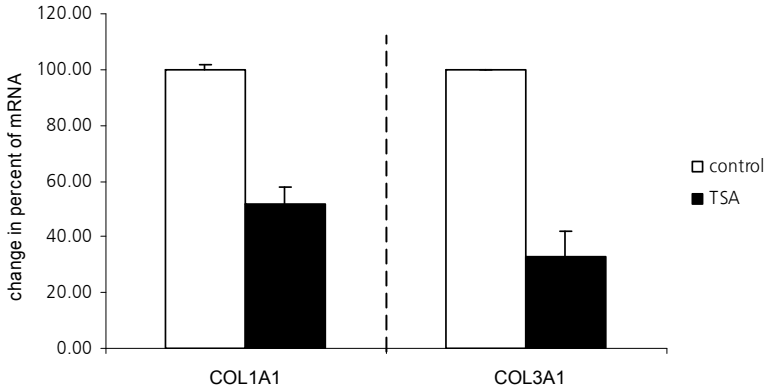

D
control
TSA
control
TSA
control
TSA
HDAC3
α-tubulin
SSc1
SSc2
SSc3
HDAC7
α-tubulin

Figure 2

A


120.00
100.00
80.00
60.00
40.00
20.00
0.00
change in percent of mRNA
COL1A1
COL3A1
control
TSA

B

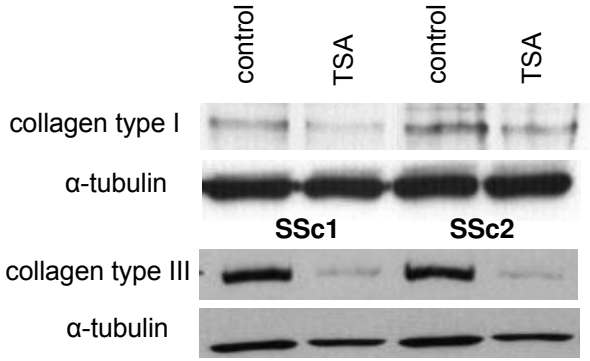

control
TSA
control
TSA
collagen type I
α-tubulin
SSc1
SSc2
collagen type III
α-tubulin

Figure 3

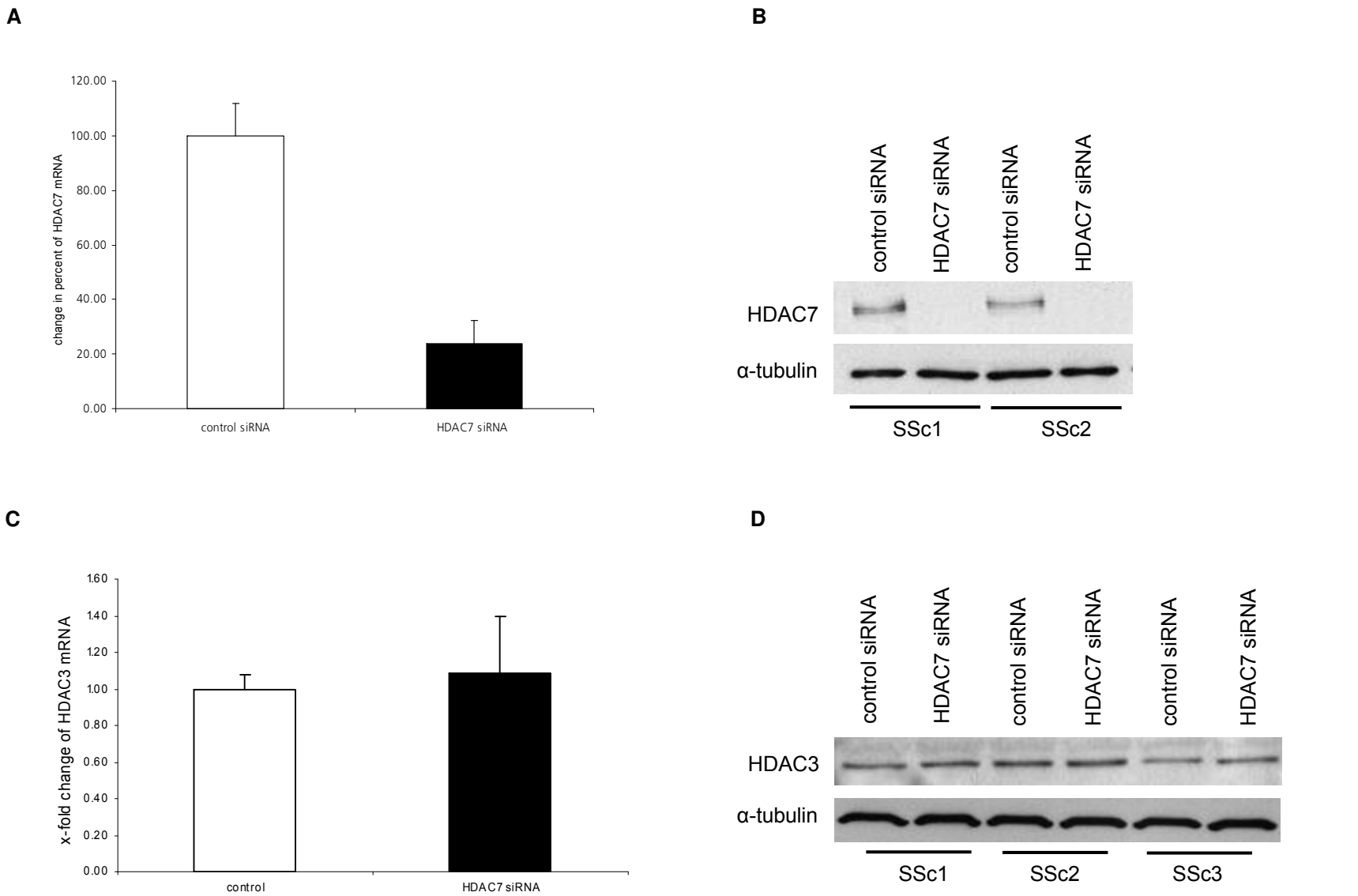

A
120.00
100.00
80.00
60.00
40.00
20.00
0.00
change in percent of HDAC7 mRNA
control siRNA
HDAC7 siRNA
B
control siRNA
HDAC7 siRNA
control siRNA
HDAC7 siRNA
HDAC7
α-tubulin
SSc1
SSc2
C
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
x-fold change of HDAC3 mRNA
control
HDAC7 siRNA
D
control siRNA
HDAC7 siRNA
control siRNA
HDAC7 siRNA
control siRNA
HDAC7 siRNA
HDAC3
α-tubulin
SSc1
SSc2
SSc3

Figure 4

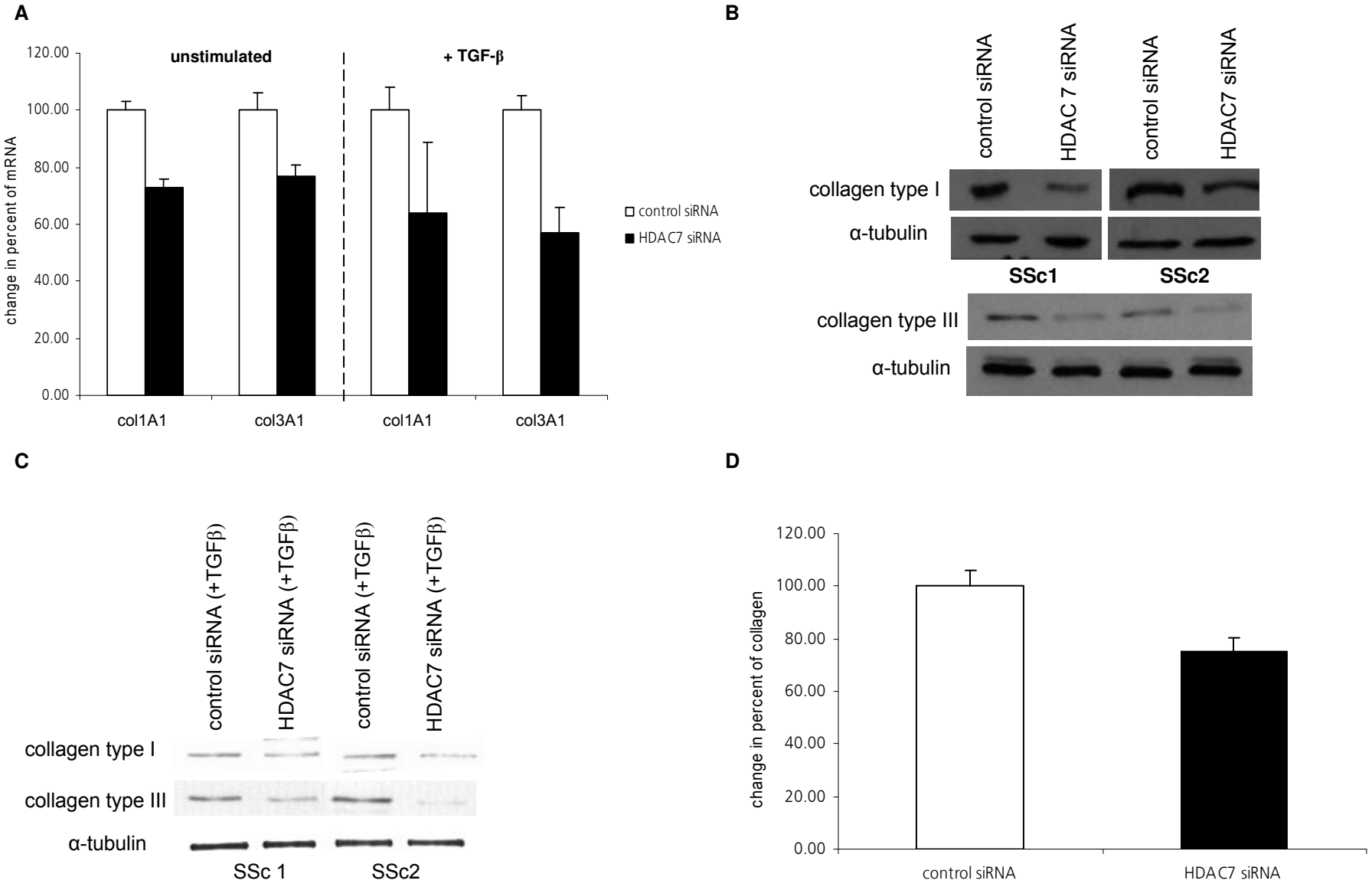

A
unstimulated
+ TGF-β
change in percent of mRNA
120.00
100.00
80.00
60.00
40.00
20.00
0.00
col1A1
col3A1
col1A1
col3A1
control siRNA
HDAC7 siRNA
B
control siRNA
HDAC 7 siRNA
control siRNA
HDAC7 siRNA
collagen type I
α-tubulin
SSc1
SSc2
collagen type III
α-tubulin
C
control siRNA (+TGFβ)
HDAC7 siRNA (+TGFβ)
control siRNA (+TGFβ)
HDAC7 siRNA (+TGFβ)
collagen type I
collagen type III
α-tubulin
SSc 1
SSc2
D
change in percent of collagen
120.00
100.00
80.00
60.00
40.00
20.00
0.00
control siRNA
HDAC7 siRNA

Figure 5

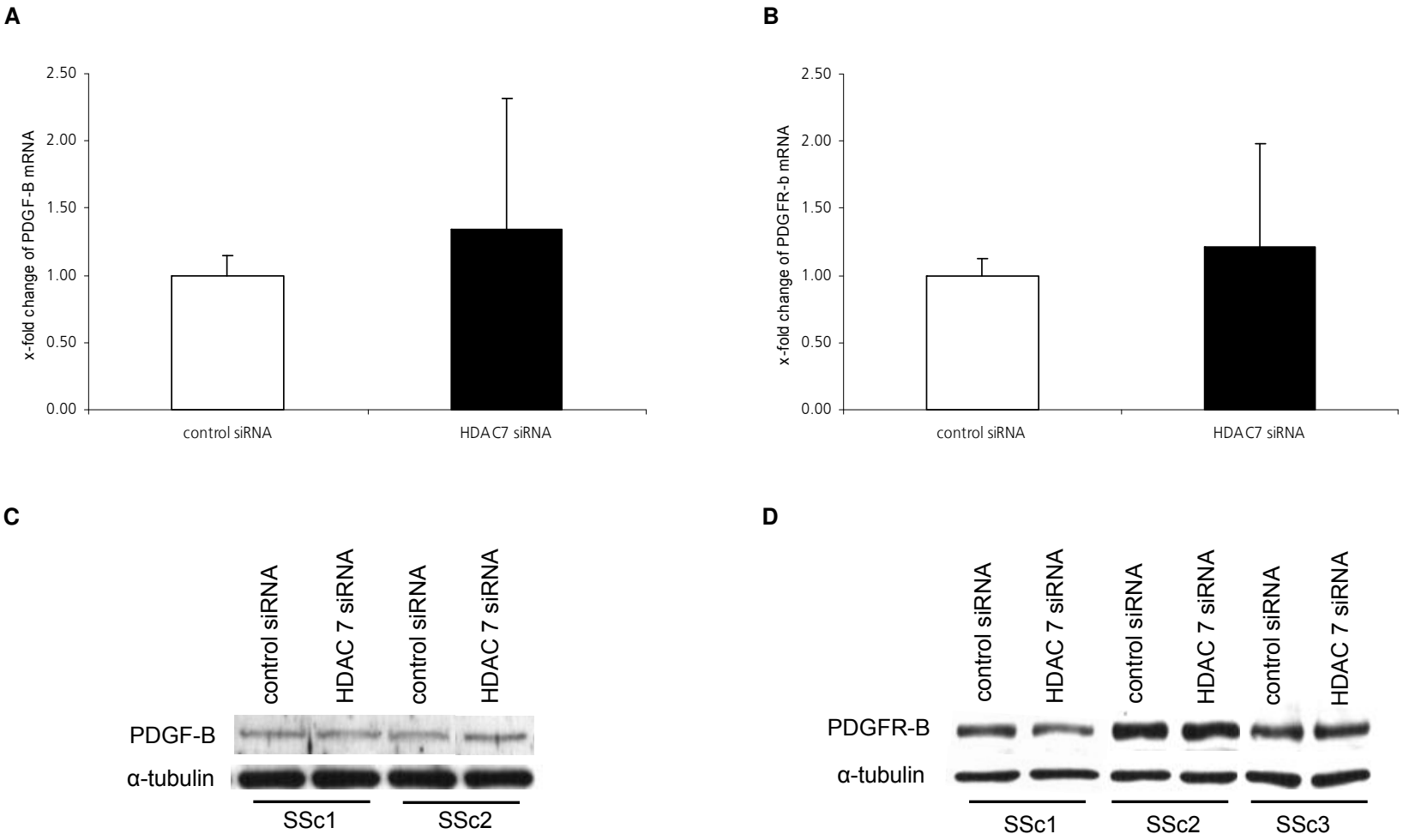
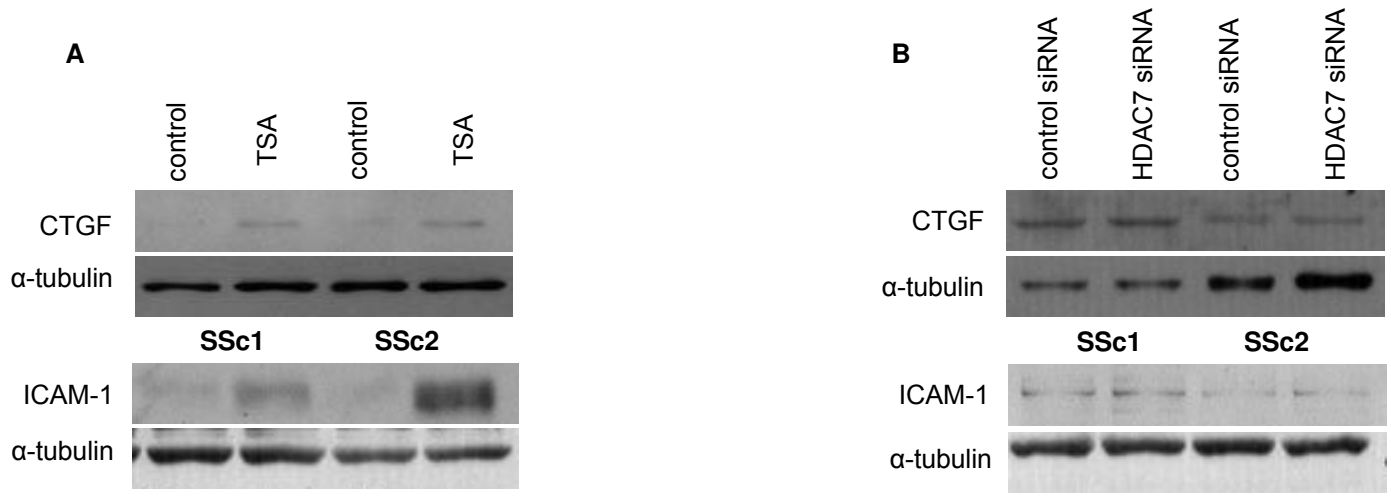

A
2.50
2.00
1.50
1.00
0.50
0.00
x-fold change of PDGF-B mRNA
control siRNA
HDAC7 siRNA
B
2.50
2.00
1.50
1.00
0.50
0.00
x-fold change of PDGFR-b mRNA
control siRNA
HDAC7 siRNA
C
control siRNA
HDAC 7 siRNA
control siRNA
HDAC 7 siRNA
PDGF-B
α-tubulin
SSc1
SSc2
D
control siRNA
HDAC 7 siRNA
control siRNA
HDAC 7 siRNA
control siRNA
HDAC 7 siRNA
PDGFR-B
α-tubulin
SSc1
SSc2
SSc3

Figure 6


A
control
TSA
control
TSA
CTGF
α-tubulin
SSc1
SSc2
ICAM-1
α-tubulin
B
control siRNA
HDAC7 siRNA
control siRNA
HDAC7 siRNA
CTGF
α-tubulin
SSc1
SSc2
ICAM-1
α-tubulin